REMARKS

1. Status of the claims

Please cancel claims 9-13, and 38-42 without prejudice to revival for subsequent prosecution in a divisional or continuation application.

With entry of the instant amendment, claims 1, 4, and 5 have been amended and claims 9-13, and 38-42 have been cancelled. Claims 7, 8, 25, and 31 were previously cancelled and claims 14-18, 34, and 35 were withdrawn by the Examiner pursuant to a restriction requirement. Accordingly claims 1-6, 19-24, 26, 30, 32, 33, 36, and 37 are currently under examination.

The amendments to the claims add no new matter and are fully supported throughout the application as filed. Claim 1 has been amended to recite a nucleic acid encoding a protein comprising an amino acid sequence having at least 95% identity to SEQ ID NO:2. Support for the amendment can be found, *e.g.*, on page 14, lines 12-31.

The rejections will be addressed in the order set forth in the Office Action mailed March 25, 2003.

Maintained rejection under 35 U.S.C. § 112, first paragraph

The rejection of the claims as allegedly lacking adequate support in the specification is maintained. The Examiner believes that the claimed sequences are not adequately enabled by the specification and cites to teachings found in Bowie, Burgess, Lazar and Bork. The original arguments presented by the Patent Office alleged that the specification does not provide support for a plurality of polynucleotides that would retain diagnostic function. The Examiner also argues that there is no evidence that the protein encoded by SEQ ID NOs 1 and 3 is expressed *in vivo*; that the references provided in the previous response are not drawn to proteins that are expressed or differentially expressed; and that one of skill would not now how to use the nucleic acid encoding SEQ ID NO:2 on page 9-10 drawn to degenerate sequences. Applicants traverse for reasons of record and for the additional reasons provided below.

SEQ ID NOs 1 and 3 express menin protein

First, the Examiner argues that one of skill in the art could not reasonably conclude that proteins encoded by SEQ ID NOs 1 and 3 are expressed. In particular, the Examiner contends that the publication (Watout *et al.*) provided in Applicants' previous response is not evidence of expression because there is no "nexus" between SEQ ID NOs 1 and 3 and the menin proteins evaluated by Watout *et al.* Applicants disagree. However, in order to expedite prosecution, Applicants submit herewith a rule 1.132 Declaration by Dr. Settara C. Chandrasekharappa, which provides additional evidence of the association between the claimed nucleic acids and expressed protein sequences. Dr. Chandrasekharappa explains that they have expressed the protein and obtained menin-specific antibodies which were used to examine protein expression in cells. He provides exemplary data in the form of a publication (Guru *et al, Proc. Natl. Acad. Sci USA* 95:1630-1634, 1998) to show that menin is localized in human cells predominantly in the nuclear fraction. The expression studies were performed using menin-specific antibodies generated to peptides comprised by SEQ ID NO:2 (see, e.g., Guru *et al*, the "Antibodies" section in "MATERIALS AND METHODS").

Dr. Chandrasekharappa also explains that Watout *et al.* describe menin polypeptide and nucleic acid sequence with reference to two publications (Chandrasekharappa *et al., Science* 276:404-407, 1997 and Guru et al.). The nucleic acid and polypeptide sequences in the two references are the same as those in the instant publication, therefore one of skill in the art understands that the protein expression analyses performed by Watout *et al.* relate to the claimed sequences.

The claimed nucleic acid sequences are useful for diagnosis and treatment of multiple endocrine neoplasia type 1.

The rejection alleges on page 3 that the references previously provided "are drawn to proteins that are not expressed or differentially expressed". This rejection appears to be based on the Examiner's belief that there is no evidence that the protein is differentially expressed in type 1 vs. type 2 multiple endocrine neoplasia. Applicants submit that the identification that *MEN1* is mutated in multiple endocrine neoplasia type 1 is compelling evidence of its role in the

disease. This assertion is supported, for example, by the *Science* publication (Chandrasekharappa et al., *supra*). The publication explicitly states that the gene of multiple endocrine neoplasia-type 1 has been cloned (*see, e.g.,* title and the last paragraph on page 406). This is a peer-reviewed article. It logically must follow that the peer-reviewers (practitioners in the art) regard the studies in the paper as establishing the role of this gene in multiple endocrine neoplasia type 1.

The Examiner also contends that Applicants did not address the issue regarding how to use nucleic acids encoding SEQ ID NO:2 in view of the lack of a known function. As asserted in the specification, exemplary uses of such nucleic acids include expression of the protein to generate antibodies, *e.g.,* for diagnostic and prognostic purposes. (See, *e.g.,* the specification on page 36, which teaches that such antibodies can be used to detect the presence of wild type or mutated menin.) Applicants have shown a number of mutations in the multiple endocrine neoplasia type 1 gene. These include frameshift, nonsense, and missense mutations (*see, e.g.,* Figures 4 and page 52, lines 18-26). The nucleic acids encoding these variant menin proteins can also be used to generate antibodies to detect mutated proteins.

The specification enables the cope of the claimed compositions

The rejection alleges that the claims are not enabled in view of Bowie, Burgess, Lazar and Bork. The cited art is described as teaching that one amino acid sequence can change function and that database searching by homology is a poor predictor of activity. The Examiner contends that these references provide evidence that one of skill in the art could not reasonably expect to identify nucleic acids encoding polypeptides having at least 95% identity to SEQ ID NO:2 as menin proteins. As previously pointed out, those of skill in the art have, in fact, identified menin proteins with this degree of identity (*see, e.g.,* Appendix E of Applicants previous response), even in the absence of knowledge of a specific function. This suggests that those of skill in the art are able to determine members of this genus of menin proteins.

In view of the foregoing, the claims are enabled and adequately supported in the specification. Applicants therefore respectfully request withdrawal of the rejection.

New grounds of objection

The amendment to the specification presented in Applciants' paper filed January 13, 2003 was rejected as additionally introducing new material. The Examiner argues that replacing "formalin with 1 mg of heparin" with "formamide" introduces new matter. The rejection alleges that "50% formalin with 1 mg heparin" is a conventional hybridization condition, based on US Patent No. 6,107,462. Applicants disagree. There is no evidence provided that recitation of this phrase in US Patent No. 6,107,462 establishes it as a conventional hybridization condition, especially when considering that it is not referred to in manuals routinely used by those in the art, such as the Sambrook manual incorporated by reference into the specification. Applicants will provide a Declaration by one of skill on the art that this would be an obvious correction, if such a Declaration will be helpful.

New ground of rejection under 35 USC § 112, first paragraph--written description

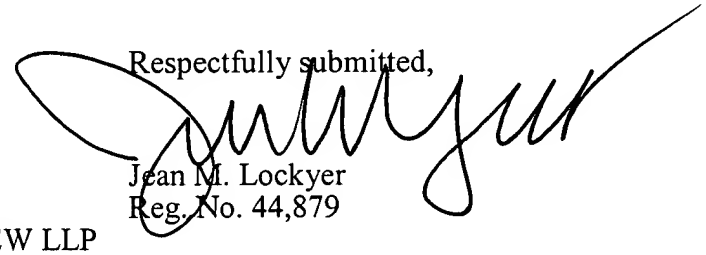
Claims 1-3, 6, 30, 32, and 33 were rejected as allegedly not adequately described in view of the hybridization conditions reciting 50% formamide. This rejection is moot in view of the claim amendments.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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